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Differentiation of Benign, Borderline and Malignant Phyllodes Tumor by Three Tiered Grading System

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Abstract: ***Background: Phyllodes tumor are rare fibroepithelial neoplasm have a morphological spectrum from benign to malignant. The risk of local recurrence is more. The diagnosis of phyllodes tumor based on histology is important as histological grading correlates with prognosis. Materials and methods: 14 cases of phyllodes tumor diagnosed in the Department of Pathology, Govt Vellore Medical College, Vellore. Phyllodes tumor are classified and histopathologically regraded as benign , borderline and malignant as per WHO 3 tiered grading system which includes stromal cellularity, cellular pleomorphism, mitosis, tumor margins, stromal overgrowth, heterologous stromal differentiation. Results: Out of 14 cases 8 cases were classified as benign, 2 cases were classified as borderline, 4 cases were classified as malignant. One case diagnosed as benign phyllodes was classified and regraded as borderline phyllodes. Other case initially diagnosed as borderline phyllodes is classified and regraded as malignant phyllodes. Another case initially diagnosed as borderline phyllodes was classified and regraded as benign phyllodes. Conclusion: Histological grading of phyllodes tumor as benign, borderline and malignant by 3 tiered grading system helps to achieve a correct diagnosis.Since stromal atypia , stromal overgrowth are independent predictors of clinical behavior. Histological features and grading was also useful in differentiating phyllodes tumor and fibroadenoma as the treatment and prognosis are different.***

Keywords: Phyllodes tumor, benign, borderline, malignant

1. Introduction

Phyllodes tumors are rare fibroepithelial neoplasm of breast. It constitutes 0.3% to 1% of all primary breast tumors and 2.5% of all fibroepithelial tumors of breast. Phyllodes tumor is a group of circumscribed biphasic tumor composed of bilayered epithelial component arranged in clefts,leaf like architecture surrounded by hypercellular mesenchymal stroma. Phyllodes tumor shows morphological spectrum between fibroadenoma and pure stromal sarcomas[1]. Interlobular or periductal stroma are the neoplastic component which determines the clinical behaviour.[2] Theories that have been proposed on the pathogenesis of Phyllodes tumors include epithelial and stromal interactions.[3]

2. Literature survey

Phyllodes tumor was referred as cystosarcoma phyllodes in literature .Johannes Muller (1838) first used the term cystosarcoma phyllodes, P*hyllodes means* leaf-like projection of the stroma into cystic spaces while *sarcoma* referred to the "fleshy" consistency of the tumour.[4],[5] In 1943 Cooper and Ackerman reported malignant behavior. In 1981, WHO adopted the term Phyllodes tumor described by Rosen. [6]Phyllodes tumor are classified into 3 subgroups as benign , borderline and malignant by histological grading .

3. Problem definition

Phyllodes tumor are rare fibroepithelial neoplasm have a morphological spectrum from benign to malignant . The risk of local recurrence is more .The diagnosis of phyllodes tumor based on histology is important as histological grading correlates with prognosis and predictive of clinical behavior.

4. Methodology and Approach

The present study was conducted retrospectively in the Department of Pathology , Govt Vellore Medical College(GVMCH), Vellore over a period of 4 years from January 2012 to December 2015.The total no of surgical biopsy specimens received in the Department of Pathology , GVMCH from January 2012 to December 2015 were 10466. Total no of breast biopsy specimens reported were 736. Out of the 736 breast biopsies 14 cases were diagnosed as phyllodes tumor.The material consisted of excision biopsy specimens and mastectomy specimens. A histopathological analysis was carried out, age, tumor size, relevant morphological details were obtained from histopathology files. The blocks and slides were retrieved from the histopathology files paraffin sections were recut, sections being 3 -4 µ thick and stained with haematoxylin and eosin. Histopathological analysis was done and phyllodes tumor were classified and regraded as benign, borderline and malignant as per WHO grading system.

5. Results

This retrospective study consisted of 14 cases of phyllodes tumor diagnosed in the Department of Pathology , Govt Vellore Medical College , Vellore .Phyllodes tumor were classified and histopathologically reevaluated and regraded as benign , borderline and malignant as per WHO 3 tiered grading system . Out of 14 cases 8cases were classified as benign, 2cases were classified as borderline ,4 cases were classified as malignant . The mean age for benign phyllodes tumor was 38.87 years (min :18years , max55 years).The mean age for malignant phyllodes tumor was 56 years (min:43 years , max 70 years). All the 8 cases of benign phyllodes tumor showed mild stromal cellularity , mitosis

ranged from 1-4/10 hpf, uniform stromal pattern and pushing margins. 4 cases of malignant phyllodes show marked stromal cellularity, mitosis 10-14/10hpf, infiltrative margins and stromal cellular pleomorphism. One case of malignant phyllodes showed heterologous element chondrosarcoma. 2 cases which did not meet all the criteria for malignancy with mitosis 5-7/10 hpf are classified as borderline phyllodes tumor. As all the cases were reevaluated and regarded as per WHO 3 tier grading system, one case showed mild to moderate stromal cellularity, moderate stromal atypia, mitosis 5 /10 hpf, tumor margins are well defined with focal infiltration and heterogenous stromal pattern initially diagnosed as benign phyllodes was classified and regraded as borderline phyllodes. Other case showed marked stromal cellularity, highly pleomorphic stromal cells, mitosis 13/10hpf, focal infiltration, marked stromal overgrowth, heterologous elements absent, it was initially diagnosed as borderline phyllodes now regraded as malignant phyllodes. Another case showed mild stromal cellularity, mitosis 2/10 hpf, uniform stromal pattern, pushing margins initially diagnosed as borderline phyllodes was classified and regraded as bening phyllodes.

Table 1: Three tiered grading subgroups for phyllodes tumor[1]

Histological features	*Benign*	*Borderline*	*Malignant*
Stromal hypercellularity	Minimal	Moderate	Marked
Cellular pleomorphism	Little	Moderate	Marked
Mitosis	0-4 /10hpf	5-9/ 10hpf	>10/ 10hpf
Margins	Pushing	Zone of microscopic invasion around tumor margins	Invasive
Stromal pattern	Uniform stromal distribution	Heterogeneous stromal expansion	Marked stromal overgrowth
Heterologous stromal differentiation	Rare	Rare	Not uncommon

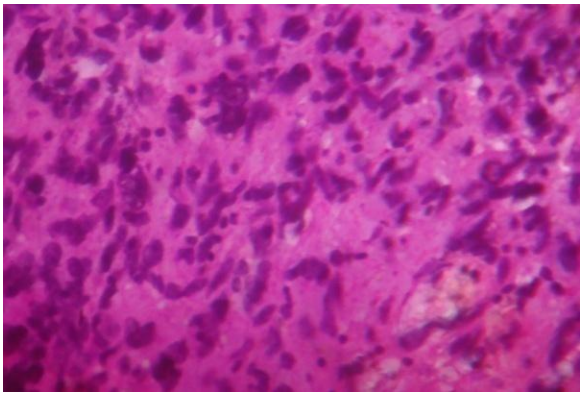

Figure 1: Malignant Phyllodes tumor. Stromal cell pleomorphism , hyperchromasia, marked stromal cellularity.

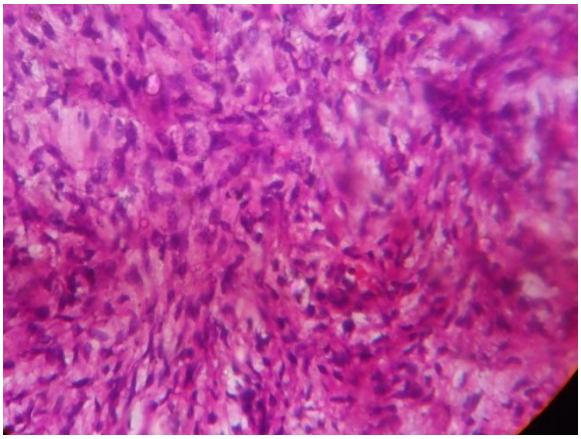

Figure 2: Borderline phyllodes. moderate stromal cellularity and atypia

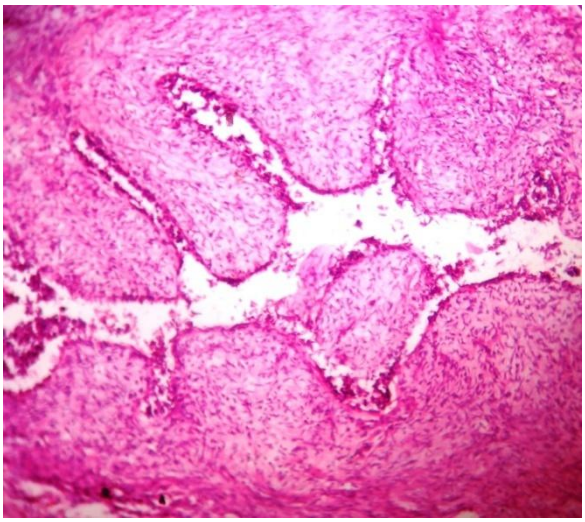

Figure 3: Boderline phyllodes: Leaf like projections, stromal overgrowth

6. Discussion

Phyllodes tumour are uncommon biphasic breast tumor which is composed of neoplastic cellular spindled stroma with benign epithelial elements. Loss of interaction between the epithelium and stroma is believed to be an important factor in the development of phyllodes tumour [7].Sub epithelial stromal areas are found to be more cellular than others. The neoplastic stromal component determines the pathological behavior. [5]Phyllodes tumor with marked stromal overgrowth and increased mitosis progress to malignancy.[7] Histological features and grading correlates with prognosis and biological attitude. Total no of phyllodes tumor reported in this study were 14. Out of which 8 cases were benign, 4 cases were malignant and 2 cases were borderline. Benign phyllodes tumor occur in a wide age group from 18 years to 55 years .Malignant phyllodes occur in older age group 2 decades later than benign phyllodes . Boderline phyllodes tumor occur between 35 – 45 years . Microscopically phyllodes tumor are characterized by leaf like architecture, cleft like spaces, benign epithelial component, cellular spindle cell neoplastic stromal component, more cellular sub epithelial stroma.[3] The benign epithelial cells line the ducts, slit like spaces and leaf like architecture. Phyllodes tumors are classified as benign ,

borderline and malignant on the basis of histological characters.

Histological parameters for the classification of phyllodes are defined [3]

1) Increased stromal cellularity is evaluated in the most cellular areas. Twice cellularity of normal perilobular stroma with even spaced nuclei, without overlapping is termed as mild. Close contiguous stromal cells with nuclei touching and overlapping is termed as marked .
2) Stromal overgrowth is defined as stromal proliferation without accompanying epithelial elements in at least 1 low power field (x4).
3) Mitosis is evaluated in more cellular areas and quantified per 10 hpf.
4) Stromal atypia – small uniform nuclei , inconspicuous nucleoli is termed as mild, marked variation in nuclear size and shape , irregular nuclear membrane , prominent nucleoli is termed as marked.
5) Projections of tumor stroma into the peritumoral stroma or adipose tissue is defined as infiltrative tumor margin.
6) Increased stromal cellularity adjacent to or underneath epithelium.

Lee et al defined the stromal cellularity as mild increase in atleast 50% of the stroma in phyllodes tumor compared with typical fibroadenoma, stromal overgrowth with no epithelium.[8] Subepithelial condensation of stromal cells is best predictor of phyllodes tumor.[8],[9] We diagnosed a case of benign phyllodes tumor presented at 18 years of age distinguished from fibroadenoma by typical leaf like pattern which is diffuse and well developed ,subepithelial condensation of stromal cells, mitosis 2 /10hpf. .Yasir et al found the average mitosis per 10 hpf was 3 in phyllodes tumor and 0.8 in fibroadenoma.[9] Thus a diagnosis of benign phyllodes tumor was done . Presence of heterologous sarcomatous elements (liposarcoma , chondrosarcoma , osteosarcoma) define a malignant phyllodes apart from marked stromal cellularity , nuclear pleomorphism, marked stromal overgrowth mitosis >10/10hpf. 4 cases of malignant phyllodes was diagnosed one case presented with heterologous component, other 3 cases showed marked stromal cellularity, nuclear pleomorphism and mitosis 10 – 14 / hpf .[3] 2 cases which do not meet all the criteria for malignant phyllodes with mitosis 5-9 /10 hpf are diagnosed as borderline phyllodes.As the grading of phyllodes is subjective the reported incidence of borderline phyllodes tumor varies [10].Phyllodes tumor with a mitotic activity of 5-9/10 hpf are clearly defined as borderline phyllodes in the WHO classification of 2012. Phyllodes tumor have high risk for local recurrences and uncommon metastasis. Local recurrence rates ranges from 10% to 40% with a average 15%.[5] Tumour grade was the only parameter related significantly to outcome and positive tumor margins are major determinant of local recurrence .[11],[12]

7. Conclusion

Phyllodes tumor show a spectrum of morphology from benign to malignant .Histological grading of phyllodes tumor as benign , borderline and malignant by 3 tiered grading system helps to achieve a correct diagnosis. Since stromal atypia, stromal overgrowth are independent predictors of clinical behaviour. Histological features and grading were also useful in differentiating phyllodes tumor and fibroadenoma as the treatment and prognosis are different . Local recurrence in phyllodes tumors has been associated with inadequate local excision and various histological characteristics including mitotic activity, positive tumor margin, and stromal hypercellularity and stromal cellular atypia.

Future scope

Histological criteria are helpful in grading phyllodes tumor and predicting the clinical behavior. Recently markers acts as adjuvants in predicting the clinical outcome.

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